

**REMARKS**

**I. STATUS OF THE CLAIMS**

After amendment, claims 1-22 are pending. Applicants amended claims 1, 4, 6-8, 11, 12, and 14-17 to correct typographical errors. Accordingly, no new matter has been added by these amendments to the claims.

**II. INFORMATION DISCLOSURE STATEMENT**

The Examiner stated that the information disclosure statement filed on October 5, 2008, "fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language." Office Action at page 2.

Applicants respectfully disagree, however, will submit English translations of the foreign patents that the Examiner noted by cross-out that she did not consider.

**III. CLAIM OBJECTIONS**

The Examiner objected to claim 17 because line 3 recites "consisting consists essentially of." Office Action at page 2. Applicants have amended claim 17 to correct this typographical error and recite "consisting essentially of." Accordingly, Applicants respectfully request that this objection be withdrawn.

**IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

The Examiner rejected claim 8 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action at page 3. Specifically, the Examiner asserts that "[t]he term 'substantially 100%' in claim 8 is a

relative term which renders the claim indefinite. The term “substantially 100%” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.” Office Action at page 3.

Applicants respectfully traverse, however, in order to expedite prosecution, Applicants amended claim 8 to delete the phrase “substantially.” Accordingly, Applicants respectfully request that this rejection be withdrawn.

#### **V. REJECTION UNDER 35 U.S.C. § 103**

The Examiner rejected claims 1-22 under 35 U.S.C. § 103 over *Tessari* (U.S. Publication No. 2002 0077589) in view of *Osman* et al. WO 00/72821 (International Application Published Under the PCT, Published 12/07/2000). The Examiner conceded that *Tessari* does not teach “that the gas comprises nitrogen. *Tessari* does not teach a mesh comprising apertures with a maximum dimension ranging from 1 to 200 microns.” Office Action at page 6. However, the Examiner asserted that *Osman* cured these deficiencies. *Id.*

According to the Examiner it would have been obvious to combine the teachings of *Tessari* and *Osman* “and utilize a mesh to pass the foam through . . . in order to produce a microfoam and one that is more uniform in nature as taught by *Osman* et al.” *Id.* at pages 6-7. Also, the Examiner concluded that it would have been obvious to combine the teachings of *Tessari* and *Osman* “and utilize a sterile pack for the apparatus. One of ordinary skill in the art would have been motivated to utilize a sterile pack in order to package and ship the formulation as well as to provide instructions for a consumer/provider on how to utilize the product.” *Id.* at page 8.

Finally, the Examiner concluded it would have been obvious to “utilize smaller amounts of nitrogen in the gas phase,” because “it is known that in the art that large volumes of nitrogen should not be introduced due to gas embolism as taught by Osman et al.” *Id.* at page 6. Further, the Examiner asserts that “Osman et al. teach nitrogen in amounts less than 40%. This includes amounts all the way to 0%. One of ordinary skill in the art would have been motivated to utilize nitrogen in low amounts based on the teachings of Osman et al. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges for nitrogen that produce expected results.” *Id.* Applicants respectfully traverse.

Applicants respectfully disagree with the Examiner that “[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges for nitrogen that produce expected results.” Even assuming a *prima facie* case of obviousness, “Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range.” *Id.* Criticality is generally shown by demonstrating that “the claimed range achieves unexpected results relative to the prior art range.” *Id.* (citing *In re Woodruff*, 919 F.2d 1575, 16 U.S.P.Q.2d 1934 (Fed. Cir. 1990)). A *prima facie* case of obviousness may also be rebutted by showing that the prior art, in any material respect, taught away from the claimed invention. *Id.* Furthermore, “a patentable invention may lie in the discovery of the source of a problem though the remedy may be obvious once the source of the problem is identified. This is part of the ‘subject matter as a whole’ which should always be considered in determining the

obviousness of an invention under 35 U.S.C. 103." *In re Spinnoble*, 405 F.2d 578, 585, 160 U.S.P.Q. 237 (C.C.P.A. 1968)

Here, even assuming that the claimed invention is *prima facie* obvious in view of *Tessari* and *Osman*, as explained herein, Applicants assert that (1) the prior art, in a material respect, taught away from the claimed invention, (2) prior to Applicants invention there was no recognition or discovery of the potential for side effects from foams made with low levels of nitrogen (e.g., 7%), and (3) it is unexpected that the instant foam achieves a result not seen using a foam with low levels of nitrogen (e.g., 7%).

**The prior art teaches away from the claimed invention**

As Applicants describe in their specification, foams made with a liquid sclerosant and **air** have been widely used to treat varicose veins in the U.S. and Europe since the late 1990's. Applicant's specification at paragraph [013]. While it was well known in the art that the use of air foams containing sclerosing agents such as polidocanol caused undesirable, and sometimes serious, side effects (including migraines, sight problems, and stroke), there was no motivation to remove essentially all nitrogen from sclerosing foams, as claimed herein, because practitioners believed that by simply lowering the amount of foam injected, they could ensure the safety of the procedure. See e.g., *Benigni*, attachment A (side effects); *Bergan*, attachment B (side effects); *Henriet*, attachment C (side effects); *Forlee*, attachment D (side effects).

This is because practitioners believed at the time (and many continue to believe today) that polidocanol is the main cause of these side effects and, therefore, they believed that injecting less foam would effectively lower the concentration of polidocanol

and remedy (or at least sufficiently lower) the risk of side effects. See *e.g.*, *Henriet*, attachment C; see *also* *Lang* declaration, attachment E. As one commentary stated:

Colleagues with a surgical background are used to treating varices patients in a single therapy session when possible. We know that this aim is often unrealistic with sclerotherapy and can only be achieved at the cost of a marked increase in the rate of adverse effects. **For this reason there is an international tendency to use smaller quantities of foam as we recommended at our European Consensus Conference back in 2003.**

*Breu*, attachment F (emphasis added). Thus, even though using less foam requires numerous, repeat treatments, the art teaches lower doses of foam as the preferred way to reduce the potential for side effects. See *e.g.*, U.S. Patent Application Publication No. US 2008/0050436 A1, attachment G at ¶ 0011 (“Due to the concerns of using too much sclerosant at one treatment, sclerotherapy generally requires multiple treatment sessions at intervals.”).

Additionally, many practitioners blamed these side effects on the use of large volumes of gases in the sclerosing foam, particularly nitrogen, which is only slightly soluble in blood. It was thought that the large volumes of gases was contributing to side effects by producing bubbles stable enough to travel to other sites, including the brain. See U.S. Patent Application Publication No. US 2008/0050436 A1, attachment G, at ¶ 0016 (“However, gas (air, CO<sub>2</sub>, etc.) is used to form the foams, and there is concern about the solubility of the gas in the body. The undissolved foams may flow to artery and other organs and cause gas embolism. If the patient has a patent foramen ovale [a hole in the heart], the foams can travel to the brain and may cause serious side effects such as stroke.”). Notwithstanding these concerns, air (comprising 80% nitrogen gas)

continues to be widely used based on the belief in the art that a lower volume is sufficient to ensure safety. Applicants specification at paragraph [014].

In sum, the prevalent solution to the issue of side effects in foam sclerotherapy taught by the prior art was to use a lower volume of foam in order to effectively lower the volume (but not concentration) of nitrogen gas and sclerosing agent. As such, practitioners did not believe that minimizing the percentage of nitrogen to the extremely low levels currently claimed (a difficult and costly process), was necessary to ensure the safety of the procedure.

Therefore, the prior art teaches away from the claimed invention and the use of very low percentages (<0.8%) of nitrogen gas in that (1) the art teaches that large volumes of foam, regardless of gas content, can be harmful, (2) air is still used predominantly in foam sclerotherapy, and (3) the art, at best, teaches lowering the volume of nitrogen gas, not the concentration, to avoid potential side effects.

**Applicants were first to recognize that even residual amounts of nitrogen in a foam could cause side effects**

Prior to Applicants invention, practitioners, including *Osman*, did not recognize that side effects could be caused even by small volumes of nitrogen gas. For example, *Osman* focuses on removing large volumes of nitrogen (less than 50%). *Osman*, noting that nitrogen gas is almost twice as insoluble in water as oxygen, states that “[f]urthermore, a problem in using air as the gas for producing the foam is the perception that large volumes of nitrogen should not be unnecessarily introduced into patients, particularly where large vessels are being filled with foam and eliminated. Gas embolism with nitrogen remains a possibility.” *Osman* at page 3, lines 6-9 (emphasis

added). Therefore, “[t]he other [than CO<sub>2</sub>] components of this gas are preferably oxygen with a minor proportion only of nitrogen being preferred.” *Osman* at page 9, lines 9-10 (emphasis added). In summary, *Osman* discloses the use of a broad range of nitrogen gas concentrations and teaches that some nitrogen gas is preferred. *Id.*

Applicants recognized, however, that simply reducing the amount of foam, and thereby the volume of nitrogen, will not necessarily solve the problem of harmful side effects. Specifically, Applicants unexpectedly found that injection of what was considered small amounts (7%) of nitrogen can result in stable bubbles that can contribute to the side effects seen with air foams.

For example, a study commissioned by Applicants, *Eckmann et al.*, reports a side-by-side comparison in rats of (a) an air based foam, (b) a foam with 7% nitrogen, and (c) a foam with 0.01-0.8% nitrogen. See *Eckmann*, attachment I. Each foam was injected into the femoral artery of the rat and the authors measured the number and size of the gas bubbles in the cremaster arterial microcirculation. *Id.* In addition, the authors observed gas bubble behavior (e.g., whether the bubbles blocked the arteries and if they did, how fast they cleared). *Id.*

*Eckmann et al.* demonstrated that injection of the air based foam (i.e., 80% nitrogen) resulted in large bubbles which lodged within the rat arterioles, obstructing blood flow *Id.* In addition, the study reported that injection of a foam containing 7% nitrogen resulted in visible bubbles in the cremaster vessels of 5 out of 6 animals, for a total of twenty-seven bubbles observed after injection. *Id.* In contrast, as discussed below, injection of a foam containing 0.01-0.8% nitrogen resulted in virtually no observable bubbles.

Therefore, Applicants were first to recognize that even small (7%) amounts of nitrogen in a foam could result in stable bubbles in the circulation that can contribute to potential side effects.

**It is unexpected that the instant foam achieves results not seen using foams of the prior art**

The *Eckmann et al.* study went on to show, surprisingly, that the very low amounts of nitrogen of the claimed invention demonstrated a visible difference in the number of bubbles circulating in rat cremaster vessels not seen with prior art foams. Specifically, in contrast to the 27 bubbles observed resulting from injection of the 7% nitrogen foam, in 5 of the 6 trials with a foam containing 0.01-0.8% nitrogen, no bubbles were observed. In the sixth trial, only two bubbles were observed. *Id.*

Therefore, the *Eckmann et al.* study unexpectedly demonstrated that the 0.01-0.8% nitrogen foam displayed distinct differences from the 7% nitrogen foam. *Id.*

Previously, practitioners believed that injection of a foam containing 7% nitrogen carried an acceptable risk of intra-arterial gas embolism and, therefore, practitioners did not believe that lowering the amount of nitrogen gas was necessary nor would it result in sufficient gains in safety to justify the added difficulty and expense of producing a foam with a nitrogen content of 0.01-0.8%. However, the Eckmann study surprisingly demonstrated that the 0.01-0.8% nitrogen foam displayed distinct differences from the 7% nitrogen foam.

Therefore, Applicants have demonstrated that (1) the prior art, in a material respect, taught away from the claimed invention, (2) there was no recognition of the potential for side effects with foams of low amounts, e.g., 7%, of nitrogen gas, and (3) it

is unexpected that the instant foam achieves a result not seen using a foam with low levels of nitrogen, and have therefore rebutted any *prima facie* case of obviousness. For at least the above reasons, Applicants respectfully request withdrawal of the rejection as to claims 1-22 under 35 USC § 103.

## **VI. DOUBLE PATENTING**

The Examiner provisionally rejected claims 1-16 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-5 and 10-12 of co-pending Application No. 10/432,328 in view of *Osman et al.* (WO 00/72821). Office Action at page 9. Specifically, the Examiner conceded that “[c]opending ‘328 does not claim that the gas contains nitrogen,” but asserted that “this deficiency is cured by *Osman et al.*” *Id.* at page 10. Applicants respectfully traverse.

The inquiry for an obviousness-type double patenting rejection tracks the obviousness determination under 35 U.S.C. § 103. Thus, for the same reasons articulated above, *Osman et al.* does not cure the deficiencies of co-pending Application No. 10/432,328. Therefore, Applicants respectfully request these rejections be withdrawn.

## **VII. CONCLUSION**

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of claims 1-22 and the timely allowance of the pending claims.

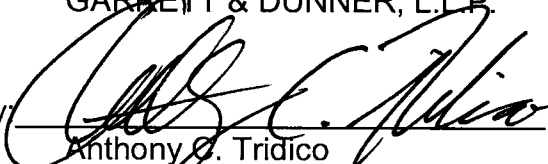
Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

Dated: March 16, 2008

By

  
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Anthony G. Tridico  
Reg. No. 45,958

Attachments:

A. *Benigni, J.P.*, Foam Sclerotherapy and Migrane with Aura, *Phlebologie*, English translation (2005).

B. *Bergan et al.*, Extensive Tissue Necrosis Following High-Concentration Sclerotherapy for Varicose Veins, *Dermatol. Surg.*, (2000) 26:535-542.

C. *Henriet, J.P.*, Three year experiment using polidocanol foam in the treatment of reticular varices and varicose veins, *Phlebologie*, English translation.

D. *Forlee et al.*, Stroke after varicose vein foam injection sclerotherapy, *J. Vasc. Surg.* (2006) 43:162-4.

E. *Lang, W.*, declaration, October 23, 2007.

F. *Breu, F.X.*, Reversible neurological complications from foam sclerotherapy, Commentary on Forlee MV et al., *Phlebologie*, English translation (2006).

G. *Chu, J.F.*, U.S. Patent Application Publication No. US 2008/0050436 A1.

H. *Frullini et al.*, Sclerosing Foam in the Treatment of Varicose Veins and Telangiectases: History and Analysis of Safety and Complications, *Dermatol. Surg.* (2002) 28:11-15.

I. *Eckmann et al.*, Microvascular Embolization Following Polidocanol Microfoam Sclerosant Administration, *Dermatol. Surg.* (2005) 31:636-643.